Remarks

Entry of this amendment is respectfully requested. Claims 56-68, 78-86, 118, and 119, are pending in the instant application. Claims 56-68, 78-86, 118, and 119 stand rejected. Claims 56, 58, 62, 78, 86, 118, and 119 are amended herein. Claims 56-68, 78-86, 118, and 119 are objected to. Applicants respectfully request reconsideration and withdrawal of the rejections for the reasons set forth herein. There is no issue of new matter.

Claim Objections

The Office Action states that Claims 58-60 stand objected to under 37 CFR 1.75(c), as being of improper dependent form failing to further limit the subject matter of a previous claim. The Examiner suggests that "[o]ne of skill in the art would recognize that an antibody heavy chain or antibody light chain comprises VH (i.e. dAb) and VL, respectively. Therefore, the recitation of dAb, VH, or VL in claims 58-59 and 60 is redundant and does not further limit independent claim 56." Applicants respectfully disagree and traverse the rejection.

Applicants assert that claims 58-60 are not redundant and do further limit the subject matter of Claim 56. Amended Claim 58 reads, "wherein said antibody heavy chain or antibody light chain polypeptides … is a domain antibody (dAb)." At the time the present invention was filed, one skilled in the art knew that Domain Antibodies (dAbs) are the smallest functional binding units of antibodies, corresponding to the variable regions of either the heavy (V_H) or light (V_L) chains of human antibodies. Therefore, Claim 58 limits the single antibody heavy chain or light chain in Claim 56 to the smallest functional binding units of a V_H or V_L (or V_k which is another type of light chain). Claim 59 and 60 states "wherein said first repertoire comprises V_H or V_L" and "wherein said second repertoire comprises V_H or V_L ", respectively. Since an antibody heavy chain or an antibody light chain comprises both variable and constant polypeptides, one skilled in the art knows that the variable regions of either the heavy (V_H) or light (V_L) chains are less than an antibody heavy chain or an antibody light chain, and more than a domain antibody (dAb).

The Office Action states that Claims 56-58, 78-86, and 118-119, are objected to because of the following informalities: independent claim 56 reads "a first repertoire of an antibody heavy chain or antibody light chain" and " a second repertoire of an antibody heavy chain or antibody light chain" which are considered grammatically incorrect. "[A] first repertoire of antibody heavy chains or antibody light chains" or a first repertoire of antibody heavy chain or antibody light chain polypeptides" and "a second repertoire of antibody heavy chain or antibody light chain polypeptides" are suggested. Please also refer to claims 58, 78, and 118-119.

Without conceding the validity of this rejection, and to further prosecution, the Applicants herein amend Claims 56, 58, 78, 118 and 119 in a manner consistent with the Examiner's suggestion and that obviates the asserted basis for this rejection. The Applicants respectfully assert that, due to the amendment, this rejection is now moot.

The Office Action further states that Claim 78 is objected to because the comma after "first" is considered a typographical error. Applicants herein amend Claim 78 to delete the comma after "first".

The Office Action further states that Claim 86 is objected to because "[t]he method of claim 56, 62, 63" is incorrect. Applicants herein amend Claim 86 to read "[t]he method of claim 56, 62, or 63".

Claim Rejections Under 35 USC § 112

The Office action states that Claim 118 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the rejection indicates that Claim 118 has insufficient antecedent basis for "third repertoire" in lines 2 and 4. The Examiner suggests changing the claim dependency from Claim 62 to claim 63.

Without conceding the validity of this rejection, Applicants have elected to present the invention in different terms, which terms obviate the asserted basis for this rejection. Applicants respectfully assert that due to the amendments made to the

existing claims, this rejection is now moot. Specifically, Applicants have amended claim 62, to include the term "third repertoire of" the target epitope. As amended, Claims 62 and 118 relate to the target epitope. Wherein Claims 63 and 119 relate to the target antigen. Therefore, Claim 118 now has sufficient antecedent basis for "third repertoire" in lines 2 and 4.

In view of the forgoing remarks, the Applicants respectfully submit that they have overcome all grounds of the Examiner's rejection under 35 U.S.C. §112, second paragraph, and that rejection should be withdrawn.

Claim Rejections Under 35 USC § 103

The Office action states that Claims 56-68, 78-86, and 118-119, are rejected under 35 U.S.C. 103(a) as being unpatentable over Feldstein et al. (U.S. Patent 6,192,168 filed April 9, 1999); Dower et al. (U.S. Patent 5,427,908 issued June 27, 1995); and McCafferty et al. (U.S. Patent 5,969,108 issued October 19, 1999). Specifically, the Examiner states that for "claims 55-57, 62-63, 65-68, and 86, Feldstein et al. teach a microfluidic device for multianalyte interactions wherein a multimode waveguide (i.e., solid surface) is paired with a fluidic cell, flow chamber, or flow cell to perform multianalyte and multisample assays comprising flowing a first set of reagents into multiple channels (i.e. continuous lines) wherein the first set of reagents is deposited on the waveguide, then placing another set of channels perpendicular (i.e. intersection, juxtaposed) to the first set of deposited reagents and flowing a second and/or third set of reagents through the channels (i.e. applied to single support of waveguide wherein the upper channels are utilized for containing fluid to prohibit mixing) wherein the first, second, and or third set of reagents can interact. (Referring to the entire specification particularly the abstract: Figures 7a-7b and 8a-8b; columns 3-13; and claims 1-31)."

The Examiner further states that for "claims 58-61 and 64, Feldstein et al. teach antibodies and antigens (i.e. heavy and light chains; referring to the entire specification particularly column 6, lines 37-67; column 7, lines 1-7; columns 10-12; claim 7)."

In addition, the Examiner concedes that "Feldstein et al. does not teach a first repertoire of antibody heavy chains and a second repertoire of antibody light chains (i.e. antibodies utilized are multimers)."

Regarding Dower et al., the Examiner states that for "claims 56, 59-61, 64, 78-85, and 118-119, Dower et al teach methods of screening single-chain polypeptides for binding comprising producing a library of antibody light chains and a library of antibody heavy chains, combining the heavy and light chains and screening for antigen binding wherein the antibody heavy and light chains are produced via phage display utilizing bacteria cells for propagation and the heavy and light chains can be expressed by the same phage or different phage (i.e. in situ production; referring to the entire specification particularly columns 3-5, 14-15; claims 1-17)."

In addition, the Examiner concedes that Feldstein et al. nor Dower et al. teach single chain polypeptides comprising both VH and VL or dAb.

Regarding McCafferty et al., the Examiner states that for "claims 56, 58-61, 78-86, and 118-119, McCafferty et al. teach methods of screening libraries of scFv and dAb for binding utilizing phage display (please refer to the entire specification particularly Figure 1; column 11; Examples 1-48)."

Finally, the Examiner states that "[t]he claims would have been obvious because the substitution of one known element (i.e. antibody; multimer taught by Feldstein et al.) for another (i.e. separate VH and VL, scFv, or dAb taught by Dower et al. and/or McCafferty et al.; utilization of scFv in sandwich assay taught by Feldstein et al.) would have yielded predictable results (i.e. VH-VL binding, antibody-antigen binding, etc.) to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the Examiner must establish that the prior art included each element claimed (M.P.E.P. 2143). In addition, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.* 167 L. Ed. 2d 705, 712. The Supreme Court in *KSR* reaffirmed the familiar framework for determining obviousness

as set forth in *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)), but stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way. However, although a rejection need not be based on a teaching or suggestion to combine, a preferred search will be directed to finding references that provide such a teaching or suggestion if they exist, especially where it is clear that the claimed invention is not a simple substitution, predictable extension or anticipated result of the prior art at the time of filing. M.P.E.P. 2141. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

The combination of Feldstein et al., Dower et al., and McCafferty et al. fails to describe each element of the claimed invention. Applicants assert that Feldstein et al. describes optical waveguide devices for detection of samples and analytes (e.g. abstract and claims) and goes on to detail multimode waveguides paired with a fluidics cell which allows optical measurements to be performed on the surface of the waveguide. The fluidics cell contains at least one channel for the flow of a fluid sample over the optically exposed region of the waveguide.

The present claims specify methods for screening a first repertoire of antibody heavy chain or antibody light chain polypeptides against a second repertoire of antibody heavy chain or antibody light chain polypeptides to identify those members of the first repertoire which interact with members of the second repertoire. There is no teaching or suggestion in Feldstein et al. of any repertoires of molecules, and certainly not

repertoires of antibody heavy and light chains and no mention of the arrangement of the repertoires as specified in the present claims.

Applicants assert that Dower et al. is in a different field to the above, which teaches using libraries of heavy and light chains of antibodies to identify binding pairs. The Examiner has not presented evidence that one having ordinary skill in the art would have been motivated to combine the teachings Dower et al. and Feldstein et al. in the proposed manner to arrive at the claimed invention. That is, there is no motivation in Dower et al. for the skilled artisan to discount the methods of Dower et al. and to adapt the teachings of Feldstein et al. to screen two repertoires to identify molecules which interact. Dower et al. provides different methods for looking at interactions between molecules to that of the present invention. For example, it describes using bacteriophage expression vectors to express Fabs and to then screen these against ligands of interest (see claim 1 of Dower). This is clearly different to the methods of the present claims which arrange the repertoires in continuous lines such that a first series comprising the first repertoire and a second series of continuous lines comprises the second repertoire and they intersect as required by the claims. Furthermore, Dower is not teaching simultaneous screening of two repertoires against each other. Rather Dower describes a simple screening method of Fabs to determine whether they react with a ligand of interest.

Similarly McCafferty et al. discloses phage display methods which are entirely different from the claimed screening methods for identifying members of specific binding pairs. There is no motivation for the skilled artisan to discount the methods of Dower and to adapt the teachings of Feldstein to screen two repertoires to identify molecules which interact. McCafferty et al. uses phage display methods for screening to identify members of specific binding pairs. Nowhere does McCafferty et al. teach or suggest screening of two repertoires against each other. This is clearly entirely different to the methods of the present claims which do screen two repertoires against each other and arrange the repertoires in continuous lines such that a first series comprises the first repertoire and a second series of continuous lines comprises the second repertoire and they intersect as required by the claims.

Thus, the claimed invention would not even have been "obvious to try" under the *KSR* standard. Accordingly, the combination of Feldstein et al., Dower et al., and McCafferty et al. references fails to teach or suggest a method for screening a first repertoire of antibody heavy chain or antibody light chain polypeptides against a second repertoire of antibody heavy chain or antibody light chain polypeptides to identify those members of the first repertoire which interact with members of the second repertoire, comprising :

a. arranging the first repertoire in at least one first series of continuous lines wherein each line of said first series comprises a member of said first repertoire and arranging the second repertoire in at least one second series of continuous lines wherein each line of said second series comprises a member of said second repertoire, wherein the first and second repertoires form an array, wherein a plurality of said first series of continuous lines intersects with a plurality of said second series of continuous lines, and wherein a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire; and

b. detecting an interaction between the antibody heavy chain or antibody light chain of the first and second repertoires, thereby identifying those members of the first repertoire that interact with members of the second repertoire.

Because the combination of Feldstein et al., Dower et al., and McCafferty et al. does not arrive at the claimed invention, a *prima facie* case of obviousness over the claims has not been established. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

The Office action states that Claims 56-58, 78-86, and 118-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowe et al. Anal. Chem. 71(2): 433-439, 1999; Stevens et al. U.S. Patent 6,485,943 filed March 22, 1999; and McCafferty et al. U.S. Patent 5,969,108 issued October 19, 1999.

The Examiner suggests that for "claims 56-57, 62-68, and 86, Rowe et al. teach methods of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor wherein vertical channels comprise antibodies and adding

samples flowed through horizontal channels (first repertoire) wherein the vertical and horizontal channels (first repertoire and/or second repertoire) wherein the vertical and horizontal channels are at 90° angles (please refer to entire reference particularly Figure 1; experimental section)." The Examiner concedes that "Rowe et al. does not specifically teach utilizing VH or VL in separate channels (i.e. multimer antibodes are utilized)."

In addition, the Examiner suggests that for "claims 59-61, Stevens et al. teach methods of making recombinant antibody subunit dimmers including VH-VL and VL-VL and screening against antigen comprising providing VH and/or VL and interacting the VH and/or VL (referring to entire specification particularly abstract; column 4, lines 44-67; column 5, lines 1-9; lines 1-9; column 6, lines 20-41; column 7, lines 23-36; columns 9-10)."

The Examiner further concedes that "neither Rowe et al. nor Stevens et al. teach dAb (i.e. specifically, VH and VL are taught by Stevens et al.) or phage display."

In addition, the Examiner suggests that for "claims 58-61, 78-86, and 118-119, McCafferty et al. teach methods of screening libraries of scFv and dAb for binding utilizing phage and propagation in bacterial cells (referring to the entire specification particularly Figure 1; column 11;Examples 1-48)."

The Examiner further suggests that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor taught by Rowe et al. with the VH-VH or VL-VL taught by Stevens et al. and the dAb and phage display taught by McCafferty et al."

The Examiner further suggests that "[o]ne having ordinary skill in the art would have been motivated to do this because Rowe et al. teach that immunosensors are easy to use, provide rapid assay times, have sensitivity comparable to ELISA, and can be utilized to study multianalyte binding (referring to introduction and conclusion sections). In addition, Stevens et al. teach homologous dimerization of antibody subunits and altering amino acid sequences in the interfacial segments to improve

yields of Fab and Fv products and studying the interactions via dimerization assay/screens (referring to columns 4-5)."

The Examiner further suggests that '[o]ne of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor taught by Rowe et al. with the VH-VH or VL-VL taught by Stevens et al. and the dAb and the phage display taught by McCafferty et al. because Rowe et al. teach utilizing immunosensors to study multianalyte interaction (e.g. VH, VL antigen, dimmers, trimers, referring to the conclusion)."

In addition, the Examiner suggests that "the claims would have been obvious because the substitution of one known element (i.e. antibodies taught by Rowe et al. and Stevens et al.) for another (i.e. antibodies displayed via phage as taught by McCafferty et al.) would have yielded predictable result (i.e. VH-VL binding, antibody-antigen binding, etc.) to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007)."

Finally, the Examiner states that "the modification of the method of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor taught by Rowe et al. with the VH-VH or VL-VL taught by Stevens et al. and the dAb and phage display taught by McCafferty et al. render the instant claims *prima facie* obvious."

In view of the Supreme Court's recent decision in *KSR Int'l v. Teleflex Inc.*, where the Examiner alleges that the claimed invention is a combination of prior art elements according to known methods, the Examiner must articulate the following:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference:
>
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each

element merely would have performed the same function as it did separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Federal Register Vol. 72, No. 195: 57256, at 57529.

"If any of these findings cannot be made, then this rationale *cannot* be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." *Id.* (emphasis added)

The hallmark of obviousness is predictability. A combination of prior art elements is obvious only if the combination does no more than yield predictable results. Conversely, it stands to reason that if the results of the combination are unpredictable (either inherently or technically), the combination is not obvious. Thus, the question to be asked in evaluating obviousness of the instant claims is not simply whether the individual elements of the claims can be found in the prior art, but whether their combination would have been predicted to yield the desired results.

In the present case, the answer to this question is no. Applicants assert that Rowe et al. teach an immunoassay performed using an immunosensor. In this immunoassay three specific chosen antibodies for detection are labelled with biotin for immobilisation to the sensor surface. These are then used to screen samples for the presence of three different analytes. This immunoassay method is different from the present invention's repertoire based screening method. Rowe et al. relates to screening of a final product/analyte by a specific antibody. It does not describe or suggest use of any repertoires of molecules and of screening these against each other, nor does it mention or suggest the checkerboard type screening of the interactions between the members of the polypeptide repertoires as described in the current application.

By contrast, Stevens et al. teach methods of making recombinant antibody dimers in which at least one codon of a nucleic acid sequence is modified (abstract) and hence is different from Rowe et al. (which describes an immunoassay using an immunosensor for detection purposes). Like Rowe et al., Stevens et al. also does not teach or suggest making any polypeptide repertoires. Were the skilled artisan to read Stevens et al. they would have likely used the methods described therein to produce antibody dimmers. For example, they would have made the specified mutations in the particular positions as described in Stevens et al. The skilled person would not have read Rowe et al., Stevens et al., and McCafferty et al. (as described above) and have been motivated to abandon these teachings and instead make repertoires of molecules as described by the present application and then screen these against one another.

In view of the foregoing remarks and claim amendments, the Applicant respectfully requests that the Examiner withdraw her rejection based on 35 U.S.C. §103.

Obviousness-type Double Patenting

The Office Action states that claims 56-68, 78-86, and 118-119 are provisionally rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1-10, 12, and 14-44 of copending Application No. 10/161,145.

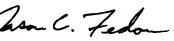
The Office Action further states that claims 56-68, 78-86, and 118-119 are provisionally rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1 and 3-23 of copending Application No. 11/413,427.

The Office Action further states that claims 56-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11, 17, and 54-70 of copending Application No. 10/008,571.

As the rejections are provisional obvious-type double patenting rejections, Applicant requests that the rejections be held in abeyance until allowable matter is indicated in one of the cases.

The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending and new claims is earnestly solicited. If it would expedite prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,



Jason C. Fedon
Attorney for Applicants
Registration No. 48,138

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-6150
Facsimile (610) 270-5090